PATENT SPECIFICATION

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COMPLETE SPECIFICATION

NO DRAWINGS

Drug Composition

We, ROHM & HAAS COMPANY, a corporation organized and existing under the laws of the State of Delaware, United States of America, of Washington Square, Philadelphia 5, State of Pennsylvania, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to a new drug composition, more particularly to a new composition of a drug embedded in plastic and suitable for oral administration.

It has always been recognized in the medical art that the administration of drugs by the oral route is to be preferred and in recent year more and more emphasis has been placed on the oral administration of drugs. There are reasons why many drugs cannot be administered satisfactorily in their simplest form. For example, the drug may be irritating to the gastro-intestinal tract and particularly to the stomach. Secondly, it may be destroyed in the stomach. Thirdly, it may be too readily absorbed with the consequent danger from toxic dosage, or it may be too readily excreted and pass out of the body before the therapeutic effect can be realized.

Numerous attempts have been made to provide a dosage from which will solve the foregoing problems, but up to the present time none of these has proved entirely satisfactory. For example, enteric coatings have been applied for many years to a wide variety of drugs in an attempt to protect the drug from gastric secretions, or to protect the stomach from the harsh effect of the drug. Enteric coatings have employed many kinds of materials and all are designed to be resistant to gastric secretions, but must be readily disintegrated in the intestinal tract in order for the drug to become effective. In every instance the enteric coating is designed to be destroyed or broken up in the intestinal tract. Enteric coatings as a class depend upon some type of chemical action or reaction for their disintegration.

Another class of protective coating for medicaments is the tyne known as time-disintegration coatings. In these coatings a class of materials is used which is dissolved or disintegrated slowly as the tablet passes through the stomach and intestine, and an amount of coating is used which is designed to allow release of the drug after a certain period of time in the body. Due to the tremendous differences in the operation of the gastro-intestinal mechanism in different persons the time-disintegration coating does not work the same way in every person but rather is designed to give results based on the mechanism of the average individual.

A variation of the time-disintegration dosage form just described is one in which particles of a medicant are coated with a varying number of layers of a material which will be slowly washed away or destroyed by the gastro-intestinal fluids. In such a dosage form a portion of the drug has little or no coating for initial response, thin coatings are used for a quick follow-up response and thicker coatings are used for a delayed response.

Time-disintegration coatings as a class depend for their disintegration upon the effects of agents found in the gastro-intestinal fluids. The enzymes, fat-solubilizers and emulsifiers in these fluids hasten the breaking-up or wearing-away of the coatings.

It is an object of the present invention, therefore, to provide an orally effective dosage form for drugs which will release an effective amount of the drug within a short time after ingestion and which will continue to release the drug slowly but uniformly

[Price 3s. 6d.]

Price 4s 6d.

Price 5s 0d

Price 75p

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over an extended period of time.

According to the present invention there is now provided a composition or small medicated mass suitable for oral administration comprising a foraminous matrix as herein defined of a solid synthetic resin carrier which is non-toxic and substantially physically inert in the presence of the gastro-intestinal fluids, and particles of a solid drug uniformly dispersed in the interstices of the matrix, whereby when the composition or mass is in the gastro-intestinal tract the drug becomes released from the matrix by leaching or diffusion over an extended period of time, e.g. eight to twelve hours. In one embodiment the drug is water-soluble and present in an amount not exceeding 60% by weight based on the total weight of the composition or mass.

The term "foraminous matrix" when used herein and in the claims appended hereto means a matrix permeable to the gastro intestinal fluids to at least a small extent sufficient to allow leaching out of most of the drug during the time that the matrix is retained by the average person. It should be noted that the degree of water permeability may be low and still be effective. For instance, foraminous matrices of polyethylene can have a very low water permeability, and yet it is satisfactory for use in this invention. One may add sodium chloride or other water-soluble electrolyte forming substance to increase the water permeability of the matrix.

When such a composition or medicated mass comes into contact with an aqueous liquid the drug is leached out or diffused out of the matrix. The amount of drug released in the early stages of the leaching out process is sufficient to provide the desired initial pharmacological response and the amount of drug released thereafter will gradually diminish over an extended period of time.

The present invention also includes a method of preparing the composition or small medicated mass according to the invention, wherein the drug in finely divided form is uniformly mixed with the carrier in particulate form and the mixture is compressed to bond together the carrier particles into a foraminous matrix having the drug uniformly dispersed in the interstices in the matrix.

The term "drug" is used herein in its broadest sense as indicating any substance or composition which will give a pharmacologic response. When it is said that the drug is water-soluble it is meant to indicate that the drug must be soluble in aqueous liquids to at least such an extent as to permit the leaching out or diffusion mentioned herein, but drugs which are readily soluble in water will, of course, make up the preferred group. Methamphetamine salts, para-amino benzoic acid, ephedrine, mannitol hexanitrate, amphetaimen, erythromycin, penicillin, pentobarbital, atropine, belladonna, theophylline, sex hormones, hydantoins, trimethadione, vitamins B and C. benzazoline, toluidine blue O and related drugs are representative of the broad class of drugs which may be administered in this new composition form. Naturally, drugs not normally solid could be rendered solid prior to use in preparing a composition or medicated mass according to the invention, for instance in known manner by being absorbed in a solid absorbent substance which may be in particulate form.

The resinous materials used in forming the permeable matrix in accordance with the invention are substantially physically inert to gastro-intestinal fluids, in particular are substantially insoluble therein; they are also non-toxic and can be ingested without danger. In a preferred form of the invention it is desirable to use a plastic carrier which is not only substantially water insoluble but which will be excreted substantially unchanged except for the loss of the drug therefrom.

The resin carriers suitable for use in this invention may be rubbery, glassy or crystalline, but they should be resistant to flow, sintering and "blocking". Among the more available resin carrier materials for use in the invention are:

1) polymers of acrylic esters, including solid homopolymers and copolymers of alkyl acrylates and methacrylates, such as methyl acrylate, methyl methacrylate, ethyl methacrylate, isopropyl acrylate, *tert*-butyl acrylate, butyl methacrylate, hexyl methacrylate, dodecyl arcylate, dodecyl methacrylate, cetyl methacrylate, or stearyl acrylate, or of cycloalkyl or aralkyl acrylates or methacrylates, including cyclohexyl acrylate or methacrylate and benzyl acrylate or methacrylate, or of esters of acrylic or methacrylic acid and an ether alcohol such as ethoxyethanol, butoxyethanol, cyclohexoxythanol, phenoxyethanol, or benzoxyethanol, and copolymers of one or more acrylic esters and another monovinyllidene compound,

2) polymers of acrylonitrile and methacrylonitrile and copolymers based in substantial parts thereon together with another polymerizable monovinylidene compound,

3) polymers of styrene, *p*-methylstyrene, or α-methylstyrene, and copolymers with other monovinylidene compounds.

4) polymers of ethylene and copolymers of ethylene and polymerizable monovinylidene compounds compatible therewith, butadiene polymers, polyfluoroethylenes,

5) polyvinyl chloride and copolymers of vinyl chloride and vinyl carboxylates such

as vinylacetate or vinyl propionate, and copolymers with other types of monovinylidene compounds,

6) polyvinylidene chloride and copolmers of vinylidene chloride and other polymerizable monovinylidene compounds, such as acrylic esters enumerated above,

7) polyvinyl acetals, including polyvinyl formal, polyvinyl acetal, or polyvinyl butyral, and copolymers formed with other vinylidene compounds,

8) polyvinyl esters of monocarboxylic acids, including acetic, propionic, butyric, lauric, or stearic, and copolymers with other types of monovinylidene compounds,

9) linear condensation polymers of alkylene succinates or alkylene terephthalates, particularly ethylene succinate or terephthalate, alkylene adipamides, omega-hydroxyalkanoic acids, omega-aminocarboxylic acids, including such lactams as caprolactam, and

10) water-insoluble cellulosic materials, such as cellulose acetate, cellulose propionate, cellulose acetatepropionate, ethyl cellulose, or methyl cellulose.

There may also be used copolymers of one or more of the above monovinylidene monomers and a comonomer such as dimethyl itaconate, diethyl itaconate, a vinyl ether such as butyl vinyl ether, or ethoxyethyl vinyl ether, N-vinyl pyrrolidinone, acrylamide, N-methylacrylamide, N-ethylmethacrylamide, acrylic or methacrylic acid, and other polymerizable monovinylidene compounds. There may also be used as comonomers small proportions of polyvinylidene compounds, particularly where there is a difference in the ease with which the several unsaturated linkages enter into polymerization. There can then be formed a thermoplastic polymer into which a drug can be dispersed even though ultimately there is developed cross-linking.

The resin carriers can be prepared by bulk, solution, suspension, or emulsion polymerization. If the last method is used, the polymer may be coagulated into solid particles which can be readily mixed with a drug or a drug may be admixed before coagulation as will be more fully discussed below.

In the polymerization procedure, it is desirable in some cases to use a step or steps in which impurities, if present, are removed. There should be removed inhibitor, if used, residual monomer or monomers, and any remaining polymerization initiator. Methods for accomplishing these ends are known in the art. They include distillation in its various aspects such as distillation with steam or under low pressure, washing and extraction.

The composition of this invention is described as having particles of a solid drug uniformly dispersed in a foraminous matrix, and the amount of drug which is dispersed in the matrix may be varied at will from a small but significant amount capable of giving a pharmacological response (5 milligrams in the case of methamphetamine) up to the saturation point beyond which the composition or medicated mass will no longer have its characteristic properties as a matrix of synthetic resin. In one embodiment up to 60% by weight of drug based on the total weight of the composition or mass can be employed. It will be apparent that the concentration of the drug and the water permeability of the matrix provide a great deal of control over the response of the drug and may be inter-related in such a way as to give the compounder wide scope in the preparation of tailored compositions and medicated masses of the invention.

A composition or mass according to the present invention may be prepared by thoroughly blending a synthetic resin carrier in powder form with the drug in crysalline or granular form and then subjecting the mixture to pressure and, if desired, heat, to convert the resin carrier into a solid body or mass having the drug dispersed therein.

In a modification of this method, a solid mass of a resin carrier having a drug dispersed therein is comminuted by grinding, shaving or other means to a small particle size and the comminuted mass is formed into a tablet with the aid of one or more tabletting adjuvants. It will be apparent, of course, that the tabletting procedure should be controlled, for example by the use of suitable tabletting adjuvants and lubricants, so that the resin does not become sintered.

The solid resinous mass having the drug dispersed therein which is used as the starting point of this modified procedure can be prepared by compression of a blended mixture of a solid, finely divided, drug and a resin carrier in particulate form, or in other ways. Thus the drug can be dispersed in a liquid monomer and the latter then polymerized, thereby achieving an excellent dispersion of the drug in the resinous mass obtained, which is then comminuted to the desired size. This method may be varied by using mixtures of monomers, and by adding polyfunctional monomers, which result in a cross-linked resin, insoluble in most solvents. By means of this latter technique, normally water-soluble polymers and very hydrophilic polymers, such as polyacrylic acid, may be employed in the invention. A solid resinous mass which is already sub-divided to a certain extent can be obtained by suspending a drug of limited water solubility which has been finely ground in a latex or aqueous dispersion of an appropriate resin. The latex is then coagulated by known procedures to give a finely divided "crumb" in which the resin

and drug are intimately associated. Alternatively, a dispersion or solution of a drug in such a latex may be spray dried or drum dried and the solid product ground and screened to give a comminuted material suitable for tabletting.

In order that the invention may be more fully understood, the following example is given by way of illustration only.

EXAMPLE

Tablets are made up according to the following directions, the amounts being on a per tablet basis:

Methamphetamine 20% by weight uniformly dispersed in polyethylene particles 10-16 mesh	75 mg.
Lactose	300 mg.
Starch	30 mg.
Water	1 cc.
Talc	16 mg.
Starch, dry	60 mg.
Magnesium stearate	4 mg.

Prepare a granulation of the lactose with a starch paste comprising the 30 mg. of starch and the water. Pass through a 4-mesh screen, dry and press through a 16-mesh screen. Blend the talc, the dry starch and the magnesium stearate, and pass through a 40-mesh screen. Combine the lactose granulation, the particles of drug-in-resin and the lubricants and compress into tablets. In the tablets so obtained the particles of drug are dispersed in the resin in accordance with the invention, that is to say in interstices in a matrix formed by the resin during compression.

WHAT WE CLAIM IS:—

1. A composition or small medicated mass, suitable for oral administration, comprising a foraminous matrix as herein defined of a solid synthetic resin carrier which is non-toxic and substantially physically inert in the presence of the gastro-intestinal fluids, and particles of a solid drug uniformly dispersed in the interstices of the matrix, whereby when the composition or mass is in the gastro-intestinal tract the drug becomes released from the matrix by leaching or diffusion over an extended period of time, e.g. eight to twelve hours.

2. A composition or small medicated mass according to Claim 1, wherein the drug is water soluble.

3. A composition or small medicated mass according to Claims 1 or 2, wherein the drug is present in an amount not exceeding 60% by weight based on the total weight of the composition or mass.

4. A composition or small medicated mass according to any one of Claims 1 to 3, wherein the drug is methamphetamine.

5. A composition in unit dosage form or small medicated mass according to Claim 4, wherein at least 5 milligrams of methamphetamine are present.

6. A composition or small medicated mass according to any one of Claims 1 to 5, wherein the carrier is polyethylene, a water insoluble polyacrylate or polymethacrylate or a copolymer of an acrylate with a methacrylate.

7. A composition or small medicated mass according to Claim 6, wherein the carrier is a copolymer of an alkyl acrylate with an alkyl methacrylate.

8. A composition or small medicated mass according to Claim 7, wherein the alkyl acrylate is methyl acrylate and the alkyl methacrylate is methyl methacrylate.

9. A small medicated mass according to any one of Claims 1 to 8, wherein the drug and carrier mass has been comminuted and reformed into a small medicated mass with one or more tabletting adjuvants.

10. A method of preparing a composition or small medicated mass according to any one of Claims 1 to 9, wherein the drug in finely divided form is uniformly mixed with the carrier in particulate form and the mixture is compressed to bond together the carrier particles into a foraminous matrix having the drug uniformly dispersed in the interstices in the matrix.

11. A method according to Claim 10, wherein the bonded mass of carrier particles with the drug uniformly dispersed therein is comminuted to small particle size and the comminuted mass is formed into a small medicated mass with the aid of one or more tabletting adjuvants.

12. A composition or small medicated mass according to any one of Claims 1 to 9, substantially as herein described with particular reference to the Example.

13. The methods of preparing a composition or small medicated mass claimed in Claim 12, as herein described.

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